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(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : RORK, Gerald, S. [US/US]; Rural Route 5, Box 274-B, Lawrence, KS 66046 (US). HASLAM, John, L. [US/US]; Rural Route 2, Lawrence, KS 66046 (US).

(74) Agent: BIGLEY, Francis, P.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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(54) Title: CONTROLLED POROSITY OSMOTIC ENALAPRIL PUMP

(57) Abstract

The instant invention is directed to an osmotic pump, for the controlled release of enalapril to an environment of use, the pump comprising: (A) a core, which comprises a therapeutically effective amount of enalapril, sodium bicarbonate, and lactose surrounded by (B) a rate controlling water insoluble wall, having a fluid permeability of 6.96×10^{-18} to 6.96×10^{-14} cm^3 sec/g and a reflection coefficient of less than 0.5, prepared from: (i) a polymer permeable to water but impermeable to solute and (ii) 0.1 to 60 % by weight, based on the total weight of (i) and (ii), of at least one pH insensitive pore forming additive dispersed throughout the wall.

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TITLE OF THE INVENTION

CONTROLLED POROSITY OSMOTIC ENALAPRIL PUMP

BACKGROUND OF THE INVENTION

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor prodrug which is orally administered. After ingestion, enalapril is hydrolyzed to enalaprilat which inhibits ACE in human subjects and other animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion.

Controlled delivery devices for therapeutically active agents are well known in the art. Generally, these devices may be characterized as either diffusion controlled delivery systems or osmotic dispensing devices. U.S. Patent 3,538,214 discloses a diffusion controlled device in which a tablet core containing an active ingredient is surrounded by a water insoluble coating which contains a film modifying agent soluble in the external fluids in the gastrointestinal tract. An example of an osmotic device is described in U.S. Patents 3,845,770 and 3,916,899. These patents describe a core composition of an active agent and an osmotically effective solute which is enclosed by an insoluble, semipermeable wall having a release means. Numerous modifications to these types of delivery devices have been described in the art in an effort to improve their release characteristics.

The use of pore formers in substantially water impermeable polymers, such as polyvinyl chloride, is disclosed in J. Pharm. Sci. 72, 772-775 and U.S. Patent 4,244,941. The devices release the core contents by simple diffusion through the pores in the coating.

U.S. Patent 3,957,523 discloses a device which has pH sensitive pore formers in the wall.

U.S. Patents 4,256,108; 4,160,452; 4,200,098 and 4,285,987 disclose devices with pore formers in only one of at least two wall layers. These devices contain a drilled hole for the release of the core contents.

U.S. Patents 4,968,507 and 4,851,228 disclose systems which comprise an inner core compartment of osmotically active composition surrounded by an enclosing controlled porosity wall material that is substantially permeable to both solute and external fluid. These systems are osmotic dispensing devices for a broad range of therapeutically active agents. However, the delivery of a highly soluble agent from these devices at a constant rate is difficult to achieve.

U.S. Patent 4,326,525 addresses the problem of delivering an active agent from an osmotic device by incorporating into the core a buffer which enters into a proton-transfer or neutralization reaction with the agent thereby producing an aqueous soluble agent salt within the device.

BRIEF DESCRIPTION OF THE INVENTION

This invention concerns an osmotically activated system for dispensing enalapril, as the pharmacologically active agent, to biological receptor sites over a prolonged period of time. The system comprises an inner core compartment of osmotically active composition surrounded by an enclosing wall.

The core comprises enalapril, sodium bicarbonate and lactose. The wall constitutes a layer of controlled porosity that is substantially permeable to both the external fluid from the environment of use and the aqueous solution which forms within the core.

Enalapril, sodium bicarbonate, and the osmotically active excipient are released from the osmotically activated system in a nearly pH independent manner by external fluid imbibition through the wall into the inner core compartment at a rate controlled by the thickness and degree of porosity in the wall. A solution containing the components of the core is released through the wall at a controlled rate in response to fluid volume flux, dV/dt, resulting from the osmotic

pressure gradient, and diffusive flux, $(dM/dt)_{diff}$, driven by the chemical potential gradient of the core composition across the wall. The total rate of release, $(dM/dt)_{total}$, is given by Equation 1 where C is the concentration

$$(dM/dt)_{total} = (dV/dt)C + (dM/dt)_{diff} \quad \text{Eq.1}$$

of the active agent in the dissolved core composition and remains constant when excess solid core mass is present.

The present invention include osmotic systems that are readily manufacturable to deliver a pre-determined dose of agent at a programmed rate from compositions of matter in the varied geometries and sizes of tablets and particulates, and such related dosage forms as familiar to those skilled in the art for oral, buccal, vaginal, rectal, nasal, ocular, parenteral and related routes of administration. The invention also provides osmotic systems that deliver agent on an equivalent mass per unit surface area basis.

A BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an embodiment of the osmotic pump element (1) in tablet form having a microporous rate controlling wall (2) surrounding a core comprising enalapril (3), sodium bicarbonate (4) and lactose (5) as well as other tableting excipients which are not shown. Figure 2 shows embodiments of the osmotic pump in multi-particulate form (2a and 2b) in a solid carrier medium (7) and a hollow carrier medium (9). Both embodiments contain multiple pump elements (1) as detailed in Figure 1. The embodiments can be distinguished by the solid matrix (6) of embodiment (7) and the hollow spaces (8) of embodiment (9) which are formed by those areas of the carrier medium, not occupied by the osmotic pump elements (1).

DETAILED DESCRIPTION OF THE INVENTION

The instant invention is directed to an osmotic pump, for the controlled release of enalapril to an environment of use, the pump comprising:

(A) a core which comprises a therapeutically effective amount of enalapril, sodium bicarbonate, and lactose, surrounded by

(B) a rate controlling water insoluble wall, having a fluid permeability of 6.96×10^{-18} to 6.96×10^{-14} cm^3 sec/g and a reflection coefficient of less than 0.5, prepared from:

(i) a polymer permeable to water but impermeable to solute and

(ii) 0.1 to 60% by weight, based on the total weight of (i) and (ii), of at least one pH insensitive pore forming additive dispersed throughout the wall.

The osmotically active core composition mass may be in the form of a solid conventional tablet, as shown in Figure 1, or individual multiparticulates, as shown in Figure 2. In either configuration, the core is completely encased by the controlled porosity wall (2), as shown in Figure 1. The core is comprised of a mixture of enalapril maleate (3), sodium bicarbonate (4), lactose (5) and other inert pharmaceutically acceptable excipients, which may be osmotically effective agents. These excipients are combined with enalapril maleate, sodium bicarbonate and lactose to give the desired manufacturing and delivery characteristics.

The preferred specifications for the core are summarized below and include:

1. Core Loading (size)	-	0.05 nanograms to 5 grams or more (includes dosage forms for humans and animals)
2. Osmotic pressure developed by a solution of the core	-	about 50 atmospheres are developed from the mixture of enalapril maleate, lactose and sodium bicarbonate; however osmotic pressures greater than zero are within guidelines

In the present invention enalapril, as the active agent, when combined with an effective amount of sodium bicarbonate, lactose and excipients has the desired solubility, osmotic pressure, density, stability, and manufacturability characteristics. The effective amount of sodium bicarbonate is an amount sufficient to provide greater than 50% of the drug release zero order and stabilize the enalapril maleate of the core composition.

By "enalapril" is meant (S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline and any of its pharmaceutically active salts such as the maleate salt, hydrates and crystal forms. This compound can be synthesized using the procedure of A. A. Patchett as found in Nature 288, 280 (1980) and in U.S. Patent 4,374,829 which is herein specifically incorporated by reference.

In preparing the granulation of the core composition, about three (3) moles of sodium bicarbonate are added to the granulation for each mole of enalapril when enalapril maleate is utilized. In the presence of the granulating solvent, water, the sodium bicarbonate reacts with the acidic functional groups of the enalapril maleate and carbon dioxide is released.

There is no critical upper limit as to the total amount of enalapril plus sodium bicarbonate that can be incorporated into a core mass and typically will follow the core loading (size) specification 1.

However, the maximum amount of enalapril contained in the core composition should not exceed the amount recommended for approved therapeutic uses. The lower limit ratio of enalapril and sodium bicarbonate to other inert pharmaceutically acceptable carriers is dictated by the desired osmotic activity of the core composition, the desired time span of release, and the pharmacological activity of the active agent. Generally the core will contain 0.01% to 90% by weight or higher, of a mixture of enalapril maleate, as the active agent, lactose, and sodium bicarbonate with other inert pharmaceutically acceptable carriers.

The solubilized constituents create a water activity gradient across the wall (2) of Figure 1, resulting in osmotically actuated fluid movement constituting the osmotic pump action of the invention. Generally, the device can house from about 0.05 ng to about 5 grams or more, with individual devices containing, for example, about 25 ng, about 1 mg, about 5 mg, about 20 mg, about 500 mg, and the like.

As a specific embodiment of the present invention, the enalapril maleate in the tablet core is between about 1 and about 50 mg and the sodium bicarbonate in the core is between about 5 ug and about 25 mg.

In another specific embodiment of the present invention, the enalapril maleate in the multiparticulates is between 1 and about 20% of the total multiparticulate core mass and the sodium bicarbonate is between about 0.0075% and about 10% of the total multiparticulate. "Core mass" is defined as the mass of the particle disregarding the mass of the coating.

The controlled porosity wall of the present invention is substantially permeable to both solute and external fluid. The wall is composed of materials that maintain their physical and chemical integrity during the controlled dispensing of agent in mixture with materials that can be leached into the external fluid. The wall has a programmable fluid transmission rate which provide for controlled release of agent which is nearly free from environmental influences including pH and degree of external fluid agitation.

The wall may be composed of either insoluble, non-erodible materials mixed with leachable additives, or bioerodible materials containing leachable additives. Bioerodible materials would be selected to bioerode after a predetermined period with bioerosion occurring subsequent to the period of enalapril maleate release.

The phrase "permeable to water but impermeable to solutes" means the water permeates through the polymer preferably to solute, under a pressure differential.

Referring to Figures 1 and 2, the osmotic pump device (1) may be in the form of a single coated tablet or multiparticulate or shaped for rectal or vaginal applications. Figures 2(a) and 2(b) exemplify the osmotic pump device as multiparticulate dosage forms while Figure 1 exemplifies the osmotic pump device as a tablet. The multiparticulates may be used directly, filled into capsules or compressed into tablets or other devices as needed.

The water insoluble, permeable wall (2) of controlled porosity may be applied to osmotically active core composition masses (3) by spray coating procedures, pan coating or any other techniques used by those familiar with the pharmaceutical arts. The wall is comprised of (a) polymeric material that is insoluble in the fluids of the environment of intended use (usually water); (b) other added excipients that will dissolve in the environmental fluids and leach out of the wall. The leached wall is a sponge-like structure composed of numerous open and closed cells that form a discontinuous interwoven network of void spaces when viewed with a scanning electron microscope. This controlled porosity wall serves as both the water entry and core composition solution exit sites. The wall is permeable to both water and solutes, and as constituted in the environment of use has a small solute reflection coefficient, δ, and displays poor semipermeable characteristics when placed in a standard osmosis cell.

The specifications for the wall are summarized below and include:

1.	Fluid Permeability of the wall	6.96×10^{-18} to 6.96×10^{-14} cm^3 sec/g (equivalent to 10^{-5} to 10^{-1} $cm^3 mil/cm^2$ hr atm)
2.	Reflection Coefficient	Microporous coats to have a reflection coefficient, δ, defined as: hydrostatic pressure difference (Hp) times osmotic volume flux (O_f) divided by the osmotic pressure difference (O_p) times the hydrostatic volume flux (H_f) that is, $\delta = \frac{H_p \times O_f}{H_f \times O_p}$ where δ is less than 1, usually 0 to 0.8.

A specific embodiment of the present invention are those osmotic pumps wherein the reflection coefficient of the wall is less than about 0.5. Exemplifying this embodiment are those osmotic pumps wherein the reflection coefficient of the wall is less than about 0.1.

Additional, preferred specifications for the wall include:

1.	Plasticizer and Flux Regulating Additives	-	0 to about 50, preferably about 0.001 to about 50, parts per 100 parts wall material
2.	Wall Thickness	-	about 1 to about 1,000, preferably about 20 to about 500 microns, typically although thinner and thicker fall within the invention
3.	Microporous Nature		about 5% to about 95% pores between 10 angstroms and 100 microns diameter

4.	Pore forming Additives	about 0.1 to about 60%, preferably about 0.1 to about 50%, by weight, based on the total weight of pore forming additive and polymer, pH insensitive pore forming additive, preferably: a) about 0.1 to about 50%, preferably 0.1 to 40%, by weight solid additive b) 0.1 to 40% by weight liquid additive But no more than 60% total pore formers.

The water insoluble wall of the instant invention must not be covered on its inner or outer surface by a layer of material that is impermeable to dissolved solutes within the core during the period of pumping operation.

Any polymer film by itself permeable to water but impermeable to solutes as previously defined may be used. However, the film may be covered initially by a rapidly dissolving coat used for aesthetic purposes or containing the same or a different drug substance. Examples include cellulose acetate having a degree of substitution, D.S., meaning the average number of hydroxyl groups on the anhydroglucose unit of the polymer replaced by a substituting group, up to 1 and acetyl content up to 21%; cellulose diacetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose triacetate having a D.S. of 2 to 3 and an acetyl content of 35 and 44.8%; cellulose propionate having an acetyl content of 1.5 to 7% and a propionyl content of 2.5 to 3% and an average combined propionyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15%, and a butyryl content of 34 to 39%; cellulose acetate having an acetyl content of 2 to 99.5%, a butyryl

content of 17 to 53%, and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, cellulose triheptylate, cellulose tricaprylate, cellulose trioctanoate, and cellulose tripropionate; cellulose diesters having a lower degree of substitution and prepared by the hydrolysis of the corresponding triester to yield cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose dicaprylate and cellulose dipentanate; and esters prepared from acyl anhydrides or acyl acids in an esterification reaction to yield esters containing different acyl groups attached to the same cellulose polymer such as cellulose acetate valerate, cellulose acetate succinate, cellulose propionate succinate, cellulose acetate octanoate, cellulose valerate palmitate, cellulose acetate palmitate and cellulose acetate heptanoate.

Additional polymers that can be used for the purpose of the invention include cellulose acetate acetoacetate, cellulose acetate chloroacetate, cellulose acetate furoate, dimethoxyethyl cellulose acetate, cellulose acetate carboxymethoxypropionate, cellulose acetate benzoate, cellulose butyrate naphthylate, cellulose acetate benzoate, methyl-cellulose acetate methylcyanoethyl cellulose, cellulose acetate methoxyacetate, cellulose acetate ethoxyacetate, cellulose acetate dimethyl sulfamate, ethylcellulose, ethylcellulose dimethyl sulfamate, cellulose acetate p-toluene sulfonate, cellulose acetate methylsulfonate, cellulose acetate dipropylsulfamate, cellulose acetate butylsulfonate, cellulose acetate laurate, cellulose stearate, cellulose acetate methylcarbamate, agar acetate, amylose triacetate beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate dimethyl aminoacetate, cellulose acetate ethyl carbonate, poly (vinyl methyl) ether copolymers, cellulose acetate with acetylated hydroxyethyl cellulose hydroxylated ethylenevinylacetate, poly (ortho ester)s, polyacetals, semipermeable polyglycolic or polylactic acid and derivatives thereof, selectively permeable associated polyelectrolytes, polymers of acrylic and methacrylic acid and esters thereof, film forming materials with a water sorption of one to fifty percent by

weight at ambient temperatures with a presently preferred water sorption of less than thirty percent, acylated polysaccharides, acylated starches, aromatic nitrogen containing polymeric materials that exhibit permeability to aqueous fluids, membranes made from polymeric epoxides, copolymers of alkylene oxides and alkyl glycidyl ethers, polyurethanes, and the like. Admixtures of various polymers may also be used.

The polymers described are known to the art or they can be prepared according to the procedures in Encyclopedia of Polymer Science and Technology, Vol. 3, pages 325 to 354, and 459 to 549, published by Interscience Publishers, Inc., New York, in Handbook of Common Polymers by Scott, J. R. and Roff, W. J., 1971, published by CRC Press, Cleveland, Ohio; and in U.S. Pat. Nos. 3,133,132; 3,173,876; 3,276,586; 3,541,055; 3,541,006; and 3,546,142.

A controlled porosity wall can be generically described as having a sponge-like appearance. The pores can be continuous pores that have an opening on both faces of a microporous lamina, pores interconnected through tortuous paths of regular and irregular shapes including curved, curved-linear, randomly oriented continuous pores, hindered connected pores and other porous paths discernible by microscopic examination. Generally, microporous lamina are defined by the pore size, the number of pores, the tortuosity of the microporous path and the porosity which relates to the size and number of pores. The pore size distribution of a microporous lamina is easily observed at the surface of the material using an electron microscope. Generally, materials possessing from 5% to 95% pores and having a pore size of from 10 angstroms to 100 microns can be used.

Any pH insensitive pore forming additives may be used in the instant invention. The microporous wall may be formed in situ, by a pore-former being removed by dissolving or leaching it to form the microporous wall during the operation of the system. The pores may also be formed in the wall prior to operation of the system by gas formation within curing polymer solutions which result in voids and

pores in the final form of the wall. The pore-former can be a solid or a liquid.

The term liquid, for this invention embraces semi-solids, and viscous fluids. The pore-formers can be inorganic or organic. The pore-formers suitable for the invention include pore-formers than can be extracted without any chemical change in the polymer. Solid additives include alkali metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium benzoate, sodium acetate, sodium citrate, potassium nitrate and the like; the alkaline earth metal salts such as calcium chloride, calcium nitrate, and the like; the transition metal salts such as ferric chloride, ferrous sulfate, zinc sulfate, cupric chloride, and the like. Water may be used as the pore-former. The pore-formers include organic compounds such as saccharides. The saccharides include the sugars sucrose, glucose, fructose, mannose, galactose, aldohexose, altrose, talose, lactose, monosaccharides, disaccharides, and water soluble polysaccharides. Also, sorbitol, mannitol, organic aliphatic and aromatic alcohols, including diols and polyols, as exemplified by polyhydric alcohols, poly(alkylene glycols), polyglycols, alkylene glycols, poly(a,l)alkylenediols esters or alkylene glycols poly vinylalcohol, poly vinyl pyrrolidone, and water soluble polymeric materials.

Pores may also be formed in the wall by the volatilization of components in a polymer solution or by chemical reactions in a polymer solution which evolve gases prior to application or during application of the solution to the core mass resulting in the creation of polymer foams serving as the porous wall of the invention. The pore-formers are nontoxic, and on their removal, channels are formed that fill with fluid. The channels become a transport path for fluid. In a preferred embodiment, the non-toxic pore-formers are selected from the group consisting of inorganic and organic salts, carbohydrates, polyalkylene glycols, poly(a,l) alkylenediols, esters of alkylene glycols, and glycols, that are used in a biological environment.

The microporous materials can be made by etched nuclear tracking, by cooling a solution of flowable polymer below the freezing point with subsequent evaporation of solvent to form pores, by gas formation in a polymer solution which upon curing results in pore formation, by cold or hot stretching at low or high temperatures until pores are formed, by leaching from a polymer a soluble component by an appropriate solvent, by ion exchange reaction, and by polyelectrolyte processes. Processes for preparing microporous materials are described in Synthetic Polymer Membranes, by R. E. Kesting, Chapters 4 and 5, 1971, published by McGraw Hill, Inc.; Chemical Reviews, Ultrafiltration, Vol. 18, pages 373 to 455, 1934; Polymer Eng. and Sci., Vol. 11, No. 4, pages 284 to 288, 1971; J. Appl. Poly. Sci., Vol. 15, pages 811 to 829, 1971; and in U.S. Pat. Nos. 3,565,259; 3,615,024; 3,751,536; 3,801,692; 3,852,224; and 3,849,528.

It is generally desirable from a preparation standpoint to mix the polymer in a solvent. Exemplary solvents suitable for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall, and the materials forming the final wall. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatic, aromatics, heterocyclic solvents and mixtures thereof.

Exemplary plasticizers suitable for the present purpose include plasticizers that lower the temperature of the second-order phase transition of the wall or the elastic modulus thereof; and also increase the workability of the wall, its flexibility and its permeability to fluid. Plasticizers operable for the present purpose include both cyclic plasticizers and acyclic plasticizers. Typical plasticizers are those selected from the group consisting of phthalates, phosphates, citrates, adipates, tartrates, sebacates, succinates, glycolates, glycerolates, benzoates, myristates, sulfonamides, and halogenated phenyls. Generally, from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated into 100 parts of wall forming material.

Suitable plasticizers can be selected for blending with the wall forming materials by selecting plasticizers that have a high degree of solvent power for the materials, are compatible with the materials over both the processing and use temperature range, exhibit permanence as seen by their strong tendency to remain in the plasticized wall, impart flexibility to the material and are non-toxic to animals, humans, avians, fishes and reptiles. Procedures for selecting a plasticizer having the described characteristics are disclosed in the Encyclopedia of Polymer Science and Technology, Vol. 10, pages 228 to 306, 1969, published by John Wiley & Sons, Inc. Also, a detailed description pertaining to the measurement of plasticizer properties including solvent parameters and compatibility such as the Hildebrand solubility parameter w, the Flory-Huggins interaction parameter x, and the cohesive-energy density, CED, parameters are disclosed in Plasticization and Plasticizer Processes, Advances in Chemistry Series 48, Chapter 1, pages 1 to 26, 1965, published by the American Chemical Society. The amount of plasticizer added generally is an amount sufficient to produce the desired wall and it will vary according to the plasticizer and the materials. Usually about 0.001 part up to 50 parts of plasticizer can be used for 100 parts of wall material.

The expressions "flux regulator agent", "flux enhancing agent" and "flux decreasing agent" as used herein mean a compound that when added to a wall forming material assists in regulating the fluid permeability of flux through the wall. The agent can be preselected to increase or decrease the liquid flux. Agents that produce a marked increase in permeability to fluid such as water, are often essentially hydrophilic, while those that produce a marked decrease to fluids such as water, are essentially hydrophobic. The flux regulators in some embodiments also can increase the flexibility and porosity of the lamina. Examples of flux regulators include polyhydric alcohols and derivatives thereof, such as polyalkylene glycols of the formula H-(O-alkylene)n-OH wherein the bivalent alkylene radical is straight or branched chain and has from 1 to 10 carbon atoms and n is 1 to 500 or higher. Typical glycols include polyethylene glycols 300, 400, 600, 1500, 1540, 4000

and 6000 of the formula H-(OCH_2CH_2)n-OH wherein n is respectively 5 to 5.7, 8.2 to 9.1, 12.5 to 13.9, 29 to 36, 29.8 to 37, 68 to 84, and 158 to 204. Other polyglycols include the low molecular weight glycols such as polypropylene, polybutylene and polyamylene.

The amount of flux regulator added to a material generally is an amount sufficient to produce the desired permeability, and it will vary according to the lamina forming material and the flux regulator used to modulate the permeability. Usually from 0.001 parts up to 50 parts, or higher of flux regulator can be used to achieve the desired results.

The osmotic pump according to the present invention may also further comprise an external layer of a pharmaceutically acceptable carrier and a therapeutically effective amount of a cardiovascular agent or diuretic agent.

Illustrative of such an osmotic pump according to the present invention are those in which the cardiovascular agent is selected from alpha receptor blocking agents, alpha and beta receptor blocking agents, antianginal agents, antiarrhythmics, antiembolus agents, antihypertensives, beta blocking agents, calcium ion influx inhibitors, diuretics, digitalis, hemorheologic agents, inotropic agents, myocardial infarction prophylaxis, quinidine, cerebral vasodilators, coronary vasodilators, peripheral vasodilators, and vasopressors.

Exemplifying such an osmotic pump according to the present invention are those in which the cardiovascular agent is selected from the calcium ion influx inhibitors or diuretics. Such calcium ion influx inhibitors include but are not limited to diltiazem and its pharmaceutically active salts. Such diuretics include but are not limited to hydrochlorothiazide.

The following examples illustrate the preparation of the drug-delivery devices of this invention and their controlled release of one or more therapeutically active ingredients into an environment of use and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

EXAMPLE 1

A multiparticulate formulation of enalapril maleate was prepared as follows: enalapril maleate (120g) was placed in a beaker and a slurry of sodium bicarbonate (62.4g) and water (300 ml) was slowly added. This mixture was allowed to stir until the neutralization was complete (as evident by no further evolution of carbon dioxide). In a Hobart planetary mixer, 360g lactose, 150g corn starch and 450g Avicel® PH-101 were mixed for 5 minutes. The above solution was then added to the solids and mixed (additional water was added until an appropriate consistency was obtained).

The resultant material was extruded on a Lewa Model EXK(F)S-1 Xtruder™ using a 1.2 mm screen. The extrudate was then spheronized in a Lewa Model QJ-230 Marumerizer™ with a bottom plate speed of 1000 RPM for 10 minutes. The resultant beads were dried overnight at room temperature at 20% relative humidity, then sized using standard mesh screens.

The coating solution was prepared by placing 900 ml of acetone in an appropriate container and slowly adding 36g of cellulose acetate butyrate (grade CAB381-20) with vigorous stirring. Once the polymer was dissolved, 300ml of methanol, 10.8g triethyl citrate and a sucrose solution (10.8g sucrose dissolved in 150g water) were added.

The multiparticulates (300 ml volume, mesh size #18) were placed in an 8" pan coater (Freund® Model HCT-20 Mini Hi-Coater). The following coating parameters were used: inlet temperature 75-80°C, outlet temperature 40-45°C, pan speed 30 RPM, atomizing air 1.2-1.4 kg/cm2 and a spray rate of 8-10 ml/min. Coating was applied when the outlet temperature reached 45°C. A total of approximately 4L of coating solution was applied. The coat weight of the resultant coated beads was 36% of the total weight of the finished beads.

USP dissolution apparatus 2 was used with a bath volume of 1000 ml of water and a stir rate of 80 RPM to determine the drug release rate profile of the coated beads. Samples (1.5ml) of the dissolution medium were withdrawn over a 20 hour period and assayed for enalapril content

by HPLC. The lag time and times for 50 and 85% of drug release are given in Table I.

EXAMPLE 2

Multiparticulates were made as per Example 1 with the following coating solution modifications: 3.6g sucrose and no triethyl citrate. This batch contained fillers and actives (fillers mesh size 18, actives mesh size 14). Sufficient coat was added to obtain 85% drug released in 8-12 hours. The lag time and time for 50 and 85% drug release are given in Table I.

EXAMPLE 3

Multiparticulates were made as per Example 1 with the following coating solution modifications: 14.4g sucrose and 7.2g diethyl phthalate. The coating weight was 24% of the total weight of the finished, coated beads. The lag time and time for 50 and 85% drug release are given in Table I.

EXAMPLE 4

Multiparticulates were made as per Example 1 with the following coating solution modifications: 36g cellulose acetate butyrate (grade CAB 500-5) polymer, 9g sucrose and no triethyl citrate. The coating weight was 25% of the total weight of the finished, coated beads. The lag time and time for 50 and 85% drug release are given in Table I.

EXAMPLE 5

Multiparticulates were made as per Example 1 with the following core modifications: 60g enalapril maleate, 31.2g sodium bicarbonate, and 420g lactose. The coating weight was 21% of the total

weight of the finished, coated beads. The lag time and time for 50 and 85% drug release are given in Table I.

EXAMPLE 6

Multiparticulates were made as per Example 1 with the following core modifications: 30g enalapril maleate, 15.6g sodium bicarbonate, and 450g lactose. The coating weight was 23% of the total weight of the finished, coated beads. The lag time and time for 50 and 85% drug release are given in Table I.

TABLE I

Enalapril Maleate Release Times

Examples	Lag Time (hrs)	Time for 50% Drug Release (hrs)	Time for 85% Drug Release (hrs)
1	.75	3	10
2	1	3	8
3	0.6	2.0	5.5
4	1	4.5	13
5	1	4	11
6	2	5.5	13

EXAMPLE 7

Enalapril maleate tablet cores were prepared with dose strengths of 5, 10 and 20 mg per tablet. The range of ingredients are given in Table II.

TABLE II

Range of Ingredients for Enalapril Maleate Cores

Ingredients	mg per Tablet
Enalapril Maleate	5 to 20
Sodium Bicarbonate	2.5 to 10
Lactose	198 to 154
Starch	22.8 to 22
Pregelatinized Starch	5 to 2.2
Iron Oxide Colorants	q.s.
Magnesium Stearate	0.9 to 1.1
Water	q.s.

The ingredients listed above in appropriate batch sizes were mixed in a high intensity mixer except for the magnesium stearate and water. The water was added at 85°C with mixing at a spray rate sufficient to add all the water in 1 to 1.5 minutes. The material was then mixed for 4 minutes. The material was then discharged into a fluidized bed dryer and dried at 50°C until the moisture content was less than 1%. The dried material was milled using a Tornado Comminutor with knives forward, 1.98 mm screen at 2500 rpm. The magnesium stearate which had been passed through a 60 mesh screen was added to the milled material in a ribbon blender and mixed for 5 minutes. The lubricated granulation was compressed into tablets on a Manesty Beta Press using 5/16" deep concave punches. Tablets of 5 mg dose weighing 230 mg, 10 mg dose tablets weighing 200 mg and 20 mg tablets weighing 200 mg were prepared. Extended release tablets were prepared using these core tablets by application of a rate controlling polymer coating.

EXAMPLE 8

Core tablets prepared as described in Example 7, containing 20 mg enalapril maleate per tablet were coated in a 8" pan coater (Freund® Model HCT-20 Mini Hi-Coater) with a microporous polymer coating consisting of cellulose acetate butyrate (grade CAB 381-20) and sucrose. The coating solution was prepared by placing 900 ml of acetone in an appropriate container and slowly adding 36 g of the polymer with vigorous stirring. Once the polymer had dissolved, 300 ml of methanol was added followed by 14.4 g of sucrose dissolved in 170 ml of water. The coating solution was applied to the tablets at a rate of 12 to 14 ml per minute through an atomization spray nozzle. The inlet air was adjusted to give an outlet air temperature of 40 to 44°C. A coating thickness of approximately 290 μ was applied to the tablets. The release of drug was determined by the use of USP dissolution setup number 2 with 1000 ml of water, and a paddle rotation of 50 rpm. Samples (approximately 2 to 3 ml) of the dissolution media were taken at various times over 20 hours. The samples were assayed for enalapril by HPLC. Table III gives the lag time and the times for 50 and 85% of drug release from these tablets.

EXAMPLE 9

Core tablets were prepared as described with 20 mg of drug per tablet and coated with a different polymer than described in Example 7. The microporous coating of this example contains cellulose acetate (grade CA 394-60S), sucrose and polyethylene glycol 400. The coating solution was prepared by placing 800 ml of acetone in an appropriate container and adding 36 g of the polymer with vigorous stirring. Once the polymer had dissolved 300 ml of methanol and 7.2 g of polyethylene glycol 400 was added. A solution of 9 g of sucrose was prepared in 200 ml of water and added to the polymer solution. Tablets were coated with this solution in the pan coater by the procedure described in Example 1. Sufficient coating (350 μ) was applied to the

tablets to give a release of 85% of the drug in 8 to 14 hours. The release of drug was determined as described in Example 7. Table III gives the lag time and the times for 50 and 85% of drug release from these tablets.

EXAMPLE 10

Core tablets were prepared as described with 20 mg of drug per tablet and coated with an ethylcellulose coating. The microporous coating of this example contains ethylcellulose and sucrose. The coating solution was prepared by placing 1000 ml of acetone in an appropriate container and adding 36 g of ethycellulose (Ethocel™ 100 standard) with vigorous stirring. Once the polymer had dissolved 100 ml of ethanol and 14.4 grams of sucrose dissolved in 170 ml of water was added. Tablets were coated with this solution in the pan coater by the procedure described in Example 24. Sufficient coating (270 μ) was applied to the tablets to give a release of 85% of the drug in 8 to 14 hours. The release of drug was determined as described in Example 7. Table III gives the lag time and the times for 50 and 85% of drug release from these tablets.

EXAMPLE 11

Core tablets were prepared as described with 5 mg of drug per tablet and coated with a cellulose acetate coating. The microporous coating of this example contains cellulose acetate, sucrose and polyethylene glycol 400. The coating solution was prepared by placing 1000 ml of acetone in an appropriate container and adding 36 g of cellulose acetate (grade CA 398-30) with vigorous stirring. Once the polymer had dissolved 7.2 grams of polyethylene glycol 400 and 10.8 grams of sucrose dissolved in 200 ml of water was added. Tablets were coated with this solution in the pan coater by the procedure described in Example 7. Sufficient coating (525 μ) was applied to the tablets to give a release of 85% of the drug in 8 to 14 hours. The release of drug was

determined as described in Example 7. Table III gives the lag time and the times for 50 and 85% of drug release from these tables.

EXAMPLE 12

Core tablets were prepared as described with 10 mg of drug per tablet and coated with a cellulose acetate coating. The microporous coating of this example contains cellulose acetate, sucrose and polyethylene glycol 400. The coating solution was prepared by placing 675 ml of methylene chloride in an appropriate container and adding 36 g of cellulose acetate (grade CA 436-80S) with vigorous stirring. Once the polymer had dissolved 3.6 grams of polyethylene glycol 400, 450 ml of methanol and 9 grams of sucrose dissolved in 50 ml of water was added. Tablets were coated with this solution in the pan coater by the procedure described in Example 24. Sufficient coating was applied (435 μ) to the tablets to give a release of 85% of the drug in 8 to 14 hours. The release of drug was determined as described in Example 7. Table III gives the lag time and the times for 50 and 85% of drug release from these tablets.

TABLE III

Enalapril Maleate Release Times

Examples	Lag Time (hrs)	Time for 50% Drug Release (hrs)	Time for 85% Drug Release (hrs)
8	0.5	3.0	8.0
9	0.8	4.0	9.5
10	0.5	4.1	10.0
11	1.2	6.7	12.0
12	1.0	6.0	12.5

WHAT IS CLAIMED IS:

1. An osmotic pump, for the controlled release of enalapril including the pharmaceutically acceptable salts, hydrates and crystal forms of enalapril to an environment of use, the pump comprising:

(A) a core, which comprises a therapeutically effective amount of enalapril, sodium bicarbonate, and lactose;

(B) a rate controlling water insoluble wall, having a fluid permeability of about 6.96×10^{-18} to about 6.96×10^{-18} cm^3 sec/g and a reflection coefficient of less than about 0.5, prepared from:

(i) a polymer permeable to water but impermeable to solute and

(ii) about 0.1 to about 60% by weight, based on the total weight of (i) and (ii), of at least one pH insensitive pore forming additive dispersed throughout the wall.

2. The osmotic pump according to Claim 1 wherein the salt form of enalapril is enalapril maleate.

3. An osmotic pump according to Claim 2 wherein the enalapril maleate is combined with about 3 mole ratios of sodium bicarbonate.

4. An osmotic pump according to Claim 1 wherein the core is in the form of a tablet.

5. An osmotic pump according to Claim 4 wherein the enalapril maleate in the tablet core is between about 1 mg and about 50 mg.

6. An osmotic pump according to Claim 4 wherein the sodium bicarbonate in the tablet core is between about 5 ug and about 25 mg.

7. An osmotic pump according to Claim 1, wherein the core is in the form of a multiparticulate.

8. An osmotic pump according to Claim 7 wherein the enalapril in the multiparticulate core mass is between about 1 and about 20% of the total multiparticulate core mass.

9. As osmotic pump according to Claim 8 wherein the sodium bicarbonate in the multiparticulate core mass is between about 0.0075% and about 10% of the total multiparticulate core mass.

10. An osmotic pump according to Claim 1, wherein the pore forming additive comprises:

(a) about 0.1 to about 50%, by weight, solid additive, based on the total weight of (i) and (ii), and/or

(b) about 0.1 to about 40%, by weight, liquid additive, based on the total weight of (i) and (ii), not to exceed a total weight % of pore forming additive of about 60%.

11. An osmotic pump according to Claim 1, wherein the reflection coefficient is less than 0.1.

12. An osmotic pump according to Claim 1, further comprising:

(c) 0 to about 50 parts per 100 parts of (i) and (ii) of plasticizer and flux regulating additives.

13. An osmotic pump according to Claim 1, wherein the water insoluble wall is about 1 to about 1,000 microns thick and

wherein about 5 to about 95% of the resulting wall pores are between about 10 angstroms and about 100 microns in diameter.

14. An osmotic pump according to Claim 11 wherein the wall is about 20 to about 500 microns thick and the wall pores are between about 10 angstroms and about 100 microns in diameter.

15. An osmotic pump according to Claim 1, wherein the polymer is selected from the group consisting of cellulose esters, acylated polysaccharides, polyurethane, polymers of acrylic and methacrylic acid and esters thereof, poly (ortho ester)s, polyacetals and mixtures thereof.

16. An osmotic pump according to Claim 15, wherein the polymer is selected from the group consisting of cellulose esters and acylated polysaccharides.

17. An osmotic pump according to Claim 15, wherein the polymer is selected from the group consisting of polyurethanes and polymers of acrylic and methacrylic acid and esters thereof.

18. An osmotic pump according to Claim 15, wherein the polymer is selected from the group consisting of poly(ortho ester)s and polyacetals.

19. An osmotic pump according to Claim 1, wherein the pore forming additive is selected from the group consisting of water, alkali metal salts, alkaline earth metal salts, saccharides, aliphatic polyols, aromatic polyols and mixtures thereof.

20. An osmotic pump according to Claim 1, wherein from about 0.1 to about 50%, by weight, of the pore forming additive is used.

21. An osmotic pump according to Claim 1, wherein the pore forming additive is sucrose.

22. An osmotic pump according to Claim 1, wherein the pH insensitive pore forming additive is selected from the group consisting of polyethylene glycol, sorbitol, glucose and mixtures thereof.

23. An osmotic pump according to Claim 1, further comprising an external layer of a pharmaceutically acceptable carrier and a therapeutically effective amount of a cardiovascular agent.

24. An osmotic pump according to Claim 22 wherein the cardiovascular agent is selected from alpha receptor blocking agents, alpha and beta receptor blocking agents, antianginal agents, antiarrhythmics, antiembolus agents, antihypertensives, beta blocking agents, calcium ion influx inhibitors, digitalis, diuretics, hemorheologic agents, inotropic agents, myocardial infarction prophylaxis, quinidine, cerebral vasodilators, coronary vasodilators, peripheral vasodilators, and vasopressors.

25. An osmotic pump according to Claim 23 wherein the calcium ion influx inhibitor is selected from the group consisting of diltiazem and its pharmaceutically active salts.

26. An osmotic pump according to Claim 23 wherein the diuretic is hydrochlorothiazide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/06271

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/24
US CL :424/473
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/473, 469, 470

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Automated Patent System: osmotic, sodium bicarbonate, lactose, enalapril

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,880,631 (HASLAM ET AL) 14 NOVEMBER 1989 See column 10, line 6; column 7, line 36; column 12, lines 11-39; claims 1, 4-7 and 9-15.	1-25
Y	US, A, 4,886,668 (HASLAM ET AL) 12 DECEMBER 1989 See column 11, lines 26-40.	1-25
Y	US, A, 4,578,075 (URQUHART ET AL) 25 MARCH 1986 See column 7, line 32.	1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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"P"	document published prior to the international filing date but later than the priority date claimed		

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